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Article

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para-Selective C–H Olefination of Aniline Derivatives via Pd/S,O-Ligand Catalysis

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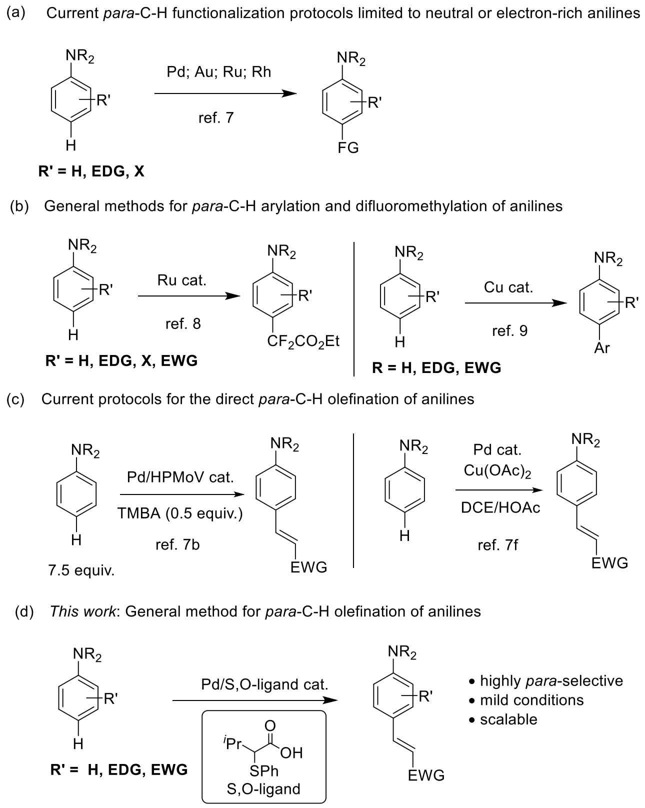
ABSTRACT: Herein we report a highly *para*-selective C–H olefination of aniline derivatives by a Pd/S,O-ligand based catalyst. The reaction proceeds under mild reaction conditions with high efficiency and broad substrate scope, including mono, di- and trisubstituted tertiary, secondary and primary anilines. The S,O-ligand is responsible for the dramatic improvements in substrate scope and the high *para*-selectivity observed. This methodology is operationally simple, scalable and can be performed under aerobic conditions.

1. INTRODUCTION

Aromatic amines are ubiquitous structural motifs in natural products, pharmaceuticals, fluorescent dyes and organic functional materials.[1] As a consequence, the selective functionalization of anilines is of great interest in organic chemistry. Historically, Friedel-Crafts reactions of aniline derivatives are problematic, as has been stated in classical textbooks.[2] Cross couplings are effective reactions for the functionalization of aromatic amines, however, these protocols suffer from the disadvantage of requiring prefunctionalized starting materials.[3] In the last decades, metal-catalyzed C–H functionalization reactions have become a powerful tool to efficiently functionalize organic molecules.[4] The vast majority of C–H functionalization reactions of aniline derivatives rely on the use of directing groups attached to the nitrogen atom, which results in the *ortho*-functionalized products.[5] However, selective C–H functionalization reactions of aniline derivatives at remote positions are rare.[6] In the particular case of metal-catalyzed *para*-selective C–H functionalization of anilines, the reported transformations are limited to unsubstituted anilines or to anilines bearing electron-donating groups (Scheme 1 a).[7] Few exceptions to this trend have been reported (Scheme 1 b). For instance, anilides with an ester group or halogen atom have been *para*-difluoromethylated using a Ru(II)-catalyst.[8] Also, a highly *para*-selective copper (II)-catalyzed arylation of electron-rich and poor anilines was described by Gaunt and coworkers.[9] In the context of Pd-catalyzed *para* C–H olefination of anilines, only two examples using unsubstituted tertiary anilines have been reported (Scheme 1c). In the example described by Ishii *et al.*,[7b] 7.5 equiv. of tertiary aniline are necessary to obtain the olefinated products in good yields and *para*-selectivities using Pd/HPMoV as catalyst and 2,4,6-trimethylbenzoic acid as an additive. In the second example, the *para*-olefination of unsubstituted *N*,*N*-dialkylanilines using Pd as catalyst, Cu as oxidant and a mixture of DCE/HOAc as solvent is reported.[7f] Therefore, a general strategy for *para*-selective C–H olefination of aromatic amines is still elusive. Herein, we report a highly efficient *para*-selective C–H olefination of aniline derivatives promoted by a Pd/S,O-ligand based catalyst (Scheme 1 d). The reaction proceeds under mild conditions with a broad range of mono-, di- and trisubstituted tertiary, secondary and primary anilines. Remarkably, anilines bearing several electron withdrawing groups are also compatible, affording the *para*-olefinated products in good yields. In addition, this *para*-selective C–H olefination of anilines is also easily scalable and is compatible with the use of oxygen as the only oxidant, which are important features for industrial applications. The S,O-ligand is responsible for the dramatic improvements in substrate scope and the high *para*-selectivity observed.

Scheme 1. Metal-Catalyzed *para*-C–H Functionalizations of Anilines

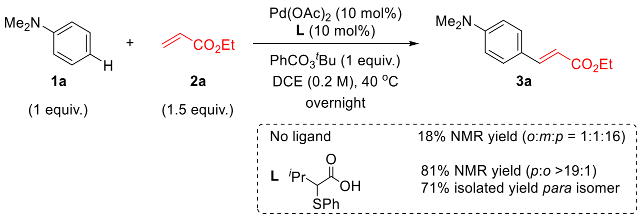


Recently, we have discovered that bidentate S,O-ligands are capable of promoting Pd-catalyzed C–H olefination reactions of nondirected arenes.[10] In these reactions, the site-selectivity was mainly dictated by the substrate and controlled by electronic factors, with preferential functionalization at the most electron-rich position in the arene. We found out that besides accelerating the reaction, the presence of the S,O-ligand influences the site-selectivity of the process. With this in mind, we speculated that using our Pd/S,O-ligand catalyst, both the reactivity and the site-selectivity of the C–H olefination of aniline derivatives could be enhanced.

2. RESULTS AND DISCUSSION

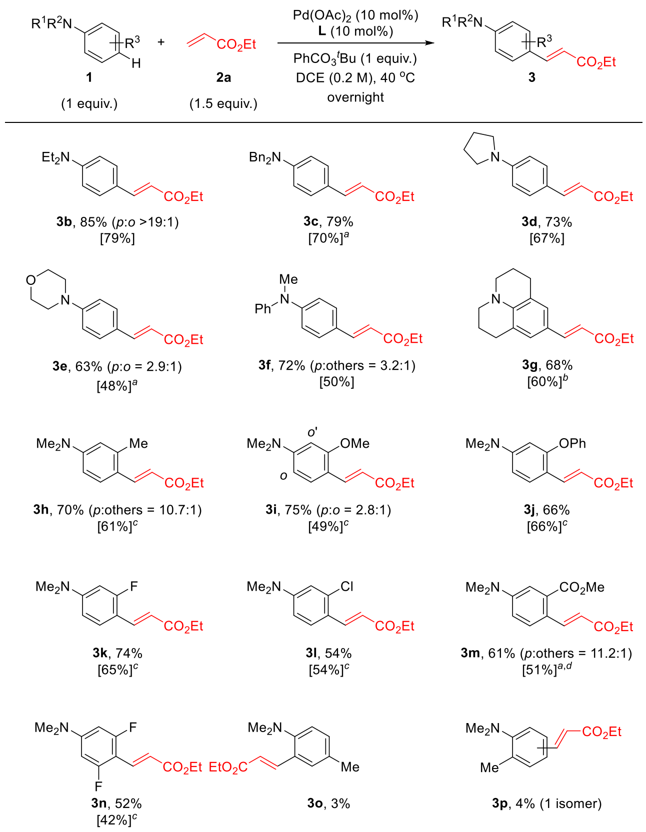
2.1. Scope of Pd/S,O-ligand catalyzed C–H olefination of aniline derivatives. Initially, we applied our standard conditions for the C–H olefination of nondirected arenes (5 mol% of $Pd(OAc)_2$, 5 mol% of 3-methyl-2-(phenylthio)butanoic acid (**L**), 10 equiv. of arene and 1 equiv. of $PhCO_3{}^tBu$ as oxidant in AcOH at 100 °C for 6 h) on the model substrate, *N*,*N*-dimethylaniline (**1a**). Unfortunately, no olefinated product was observed under these conditions. Different reaction parameters, including solvents, temperatures, reaction stoichiometries, oxidants, concentrations and ligands were screened (see Supporting Information). We were pleased to find out that the reaction of *N*,*N*-dimethylaniline (**1a**, 1 equiv.) with ethyl acrylate, using the Pd/S,O-ligand (**L**) as catalyst, in DCE at 40 °C, furnished the olefinated product **3a** in 81% NMR yield with excellent *para*-selectivity (*p*:*o* >19:1) (71% isolated yield of the *para*-olefinated product **3a**, Scheme 2). In contrast, the reaction without ligand, under the same conditions, gave the olefinated product **3a** in 18% NMR yield as a mixture of the 3 possible isomers (*o*:*m*:*p* = 1:1:16).

Scheme 2. S,O-Ligand Promoted Pd-Catalyzed *para*-Selective C–H Olefination of *N*,*N*-dimethylaniline



To investigate the substrate scope of this transformation, various aniline derivatives were examined (Table 1). We first explored the olefination reaction of several tertiary aniline derivatives. *N*,*N*-Diethyl-, *N*,*N*-dibenzylaniline and 1-phenylpyrrolidine (**1b**–**1d**) were olefinated in excellent yield (73–85%) and excellent selectivity toward their *para* positions. Good yields and slightly deteriorated selectivities were observed using 4-phenylmorpholine (**1e**) and *N*-methyldiphenylamine (**1f**). Julolidine reacted to form only the *para*-olefinated product **3g** in 60% isolated yield. Having proved the compatibility of the method with a variety of tertiary aniline derivatives, different *meta*-substituted *N*,*N*-dimethylanilines were then tested. The reaction of *m*-methyl *N*,*N*-dimethylaniline (**1h**) provided the olefinated product **3h** in good yield (70%) and *para*-selectivity (>10:1). Good yield (75%) and moderate *para*-selectivity was observed in the reaction of the *m*-methoxy *N*,*N*-dimethylaniline (**1i**). In contrast, the reaction of the *m*-phenoxy *N*,*N*-dimethylaniline (**1j**) exhibited a perfect *para*-selectivity, obtaining the product **3j** in 66% isolated yield. The corresponding *para*-olefinated products of *N*,*N*-dimethylaniline derivatives bearing electron withdrawing substituents such as F, Cl and CO_2Me (**1k**–**m**), were obtained in good yields (51–65%). Similarly, the reaction tolerated two fluorine atoms at the *meta* position of the aniline, providing the *para*-olefinated product **3n** in 42% isolated yield. Interestingly, and in accordance with the high *para*-selectivity observed in these transformations, only 3% of the *ortho*-olefinated product was detected when using *p*-methyl *N*,*N*-dimethylaniline (**1o**). To extend the substrate scope of the reaction, we tested the reaction of *o*-methyl *N*,*N*-dimethylaniline (**1p**) under standard reaction conditions, but only traces amount of product were detected by ^{1}H-NMR spectroscopy.[11]

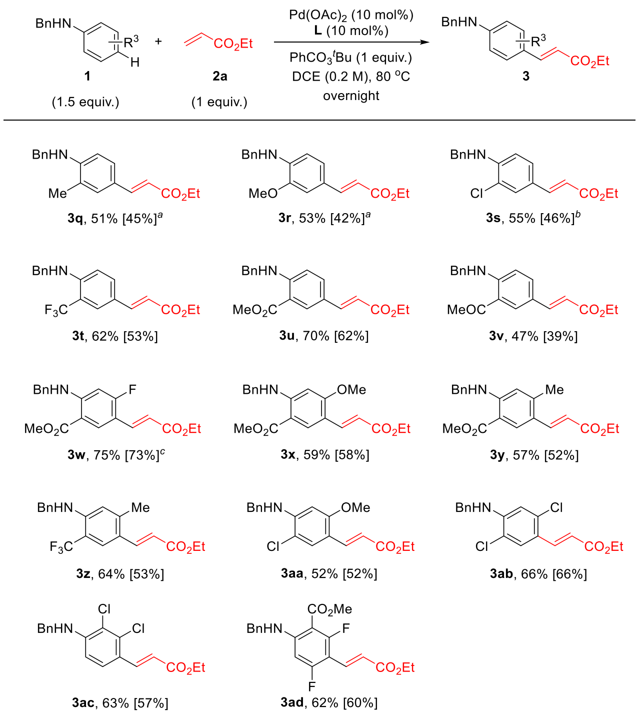
Table 1. *para*-Selective C–H Olefination of *N*,*N*-Dialkylanilines



Yields and selectivities were determined by ^{1}H NMR analysis of the crude mixture using CH_2Br_2 as internal standard. Isolated yields of *p*-isomer were given in square bracket. [a]The reaction was performed at 60 °C. [b]2 M of DCE was used. [c]0.8 M of DCE was used. [d]1.5 equiv of aniline derivative and 1 equiv of olefin were used.

Alternatively, *N*-benzyl *ortho*-substituted aniline derivatives were efficiently *para*-olefinated using our Pd/S,O-ligand based catalyst (Table 2). The reaction of *o*-Me-,OMe-,Cl-,CF$_3$-,CO$_2$Me-, and COMe-substituted *N*-benzyl aniline derivatives **1q**–**1v** exhibited perfect *para*-selectivities, providing the *para*-olefinated products in good yields (47–70%). Only traces amounts of the C–H olefinated product occurring at the *ortho* position of the benzene ring of the benzyl group were detected. In contrast, this byproduct was formed in greater quantity when the reactions were performed without ligand (see Supporting Information).

Table 2. *para*-Selective C–H Olefination of *N*-Benzylanilines

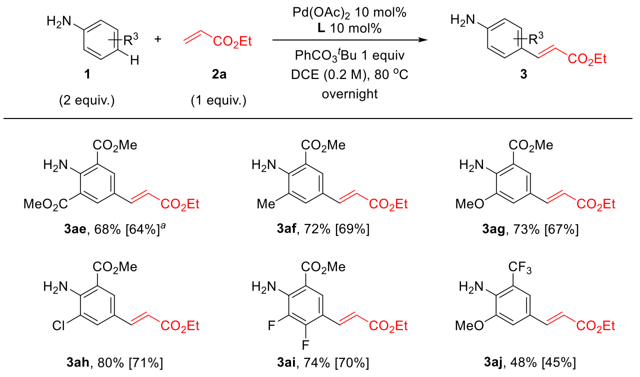


Yields and selectivities were determined by ^{1}H NMR analysis of the crude mixture using CH_2Br_2 as internal standard. Isolated yields of *p*-isomer were given in square bracket. [a]2 equiv. of aniline derivative was used. [b]0.1 M of DCE was used. [c]Yields and selectivites were determined by ^{1}H NMR analysis of the crude mixture using hexafluorobenzene as internal standard.

After proving the efficiency of the new catalytic system in anilines bearing both electron donating and withdrawing groups we evaluated a variety of di- and tri-substituted *N*-benzylaniline derivatives. Disubstituted anilines with an *ortho* methyl ester group and different substituents at the *meta*-position, i.e. F, OMe and Me, underwent C–H olefination to provide the *para*-olefinated products **3w**–**3y** in good yields (57–75%). *N*-Benzyl- *m*-methyl-*o*-(trifluoromethyl)aniline (**1z**) and *o*-chloro-*m*-methoxyaniline (**1aa**) were also compatible with this system, providing the *para*-olefinated products in 53% and 52% isolated yield, respectively. Slightly higher yields for the olefinated products **3ab** and **3ac** were obtained when 2,5-dichloro- and 2,3-dichloro aniline derivatives were used. The reaction of the trisubstituted *o*-methyl ester *m,m'*-difluoroaniline derivative provided the *para*-olefinated product **3ad** in 60% isolated yield.

Finally, we studied the compatibility of the current catalytic system with primary anilines (Table 3). We observed that the efficiency of the reaction is highly dependent on the substituents attached to the aromatic ring. The reaction of *ortho*-disubstituted anilines bearing two electron donating groups provided the olefinated product in low yields. In these reactions, we detected the formation of the oxidative amination product (see Supporting Information for further details).[12] To our delight, the olefinated products were obtained in high yields and with perfect *para*-selectivities with *ortho*-disubstituted anilines bearing one ester group at the *ortho*-position. Thus, different substituents at the other *ortho*-position such as CO$_2$Me, Me, OMe and Cl were compatible in the reaction, providing the olefinated products **3ae-3ah** in good isolated yields (64-71%). The reaction of the trisubstituted aniline **1ai** bearing two fluorine atoms and a methyl ester furnished the olefinated aniline **3ai** in 70% isolated yield. A fair yield (45%) was obtained in the reaction of the disubstituted (*o*-CF$_3$ and *o*-OMe) aniline.

Table 3. *para*-Selective C–H Olefination of primary anilines



3ae, 68% [64%][a] **3af**, 72% [69%] **3ag**, 73% [67%]

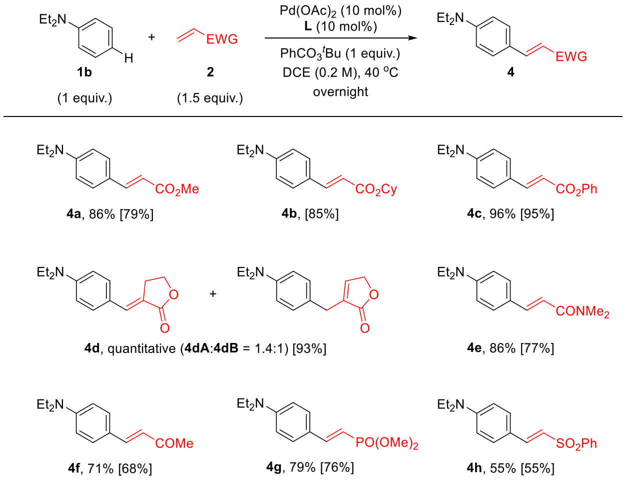
3ah, 80% [71%] **3ai**, 74% [70%] **3aj**, 48% [45%]

Yields and selectivities were determined by ^{1}H NMR analysis of the crude mixture using CH_2Br_2 as internal standard. Isolated yields of *p*-isomer were given in square bracket. [a]1.5 equiv of aniline derivative was used.

It is worth mentioning that in all these reactions (Tables 1,2 and 3), the presence of the S,O-ligand is crucial to achieve good yield and high *para*-selectivity (see Supporting Information for the results of the reactions in the absence of the S,O-ligand).

Next, we investigated the scope of olefins as depicted in Table 4. The reaction of *N*,*N*-diethylaniline with methyl, cyclohexyl and phenyl acrylates provided the products **4a**–**4c** in high yield (85–96%) and selectivity. *α*-Methylene-*γ*-butyrolactone afforded compound **4d** in excellent yield as a mixture of **4dA** and **4dB** in 1.4 to 1 ratio. Likewise, other activated olefins, i.e. vinyl amide, methyl vinyl ketone, vinyl phosphonate and vinyl sulfonate, were also employed to provide products **4e**–**4h** in good yields.

Table 4. Scope of Olefines



4a, 86% [79%] **4b**, [85%] **4c**, 96% [95%]

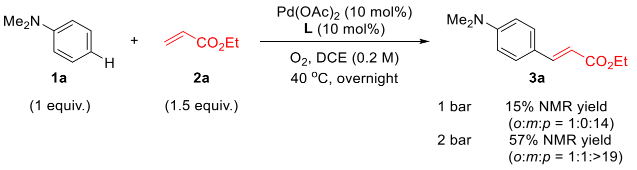
4d, quantitative (**4dA**:**4dB** = 1.4:1) [93%] **4e**, 86% [77%]

4f, 71% [68%] **4g**, 79% [76%] **4h**, 55% [55%]

Yields and selectivities were determined by ^{1}H NMR analysis of the crude mixture using CH_2Br_2 as internal standard. Isolated yields of *p*-isomer were given in square bracket.

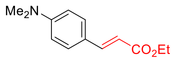
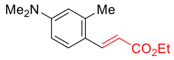
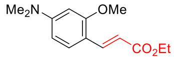
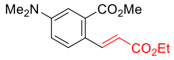
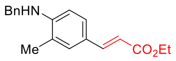
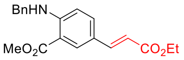
To prove the applicability of the present catalytic system, a half-gram-scale reaction of *N*,*N*-dimethylaniline (**1a**) was conducted to afford **3a** in comparable yield (64%) to that of the original value (for further details, see Supporting Information). In addition, we explored the possibility of replacing $PhCO_3{}^tBu$ by oxygen (Scheme 3). The reaction of *N*,*N*-dimethylaniline (**1a**) under otherwise identical conditions using a balloon of oxygen showed the formation of the olefinated product **3a** in 15% yield. To our delight, the reaction using 2 bar of oxygen provided the desired product in 57% yield in good *para*-selectivity. These results show the potential of this methodology to be implemented in the chemical industry.

Scheme 3. C–H Olefination of *N*,*N*-Dimethylaniline under aerobic conditions



2.2. Comparison of the Pd/S,O-ligand catalytic system with the reported catalytic systems for the *para*-C–H olefination of anilines. As mentioned in the introduction, only two examples were reported for the Pd-catalyzed *para* C–H olefination of anilines.[7b,7f] To demonstrate that this catalytic system is a unique method to olefinate a broad range of anilines we compared our catalytic system with previously described protocols. We performed the reaction of *N*,*N*-dimethylaniline with methyl acrylate under the conditions described by Moghaddam et al.,[7f] $Pd(OAc)_2$ (5 mol%), Cu(OAc)2 (1.5 equiv.) in a mixture of DCE/HOAc (1.5:1) at 60 °C; however, in our hands only trace amount of olefinated product was detected by ^{1}H-NMR spectroscopy. We then tested different anilines under the conditions described by Obora and Ishii using 7.5 equiv. of aniline, $Pd(OAc)_2$, (5 mol%), $H_6PMo_9V_3O_{40}.30H_2O$ (0.5 mol%) and 0.5 equiv. of 2,4,6-trimethylbenzoic acid in DMF (Table 5).[7b] The reaction of *N*,*N*-dimethylaniline under these conditions gave the olefinated product in good yield and with slightly lower *para*-selectivity than using our catalytic system. When we performed the reaction of *m*-methyl *N*,*N*-dimethylaniline (**1h**) only 24% ^{1}H-NMR yield and moderate *para*-selectivity (4.6:1) was observed using Ishii's conditions. Using our catalytic system we obtained the olefinated product **3h** in 70% yield and high *para*-selectivity (10.7:1). Remarkably, under Ishii's conditions, no reaction or only trace amount of product was detected when *m*-methoxy- or *m*-methyl esther *N*,*N*-dimethylaniline (**1i, 1m**) were employed. Similarly, the reaction of *N*-benzyl *ortho*-substituted anilines (**3q** and **3u**) under Ishii's conditions provided only trace amount of product in contrast to our catalytic system that furnished the olefinated products in good yields and perfect *para*-selectivities. Overall, Ishii's conditions are suitable for the olefination of unsubstituted tertiary anilines and therefore, we can confirm that our catalytic system based on Pd/S,O-ligand is at present the only efficient protocol for the direct C–H olefination of a broad range of anilines.

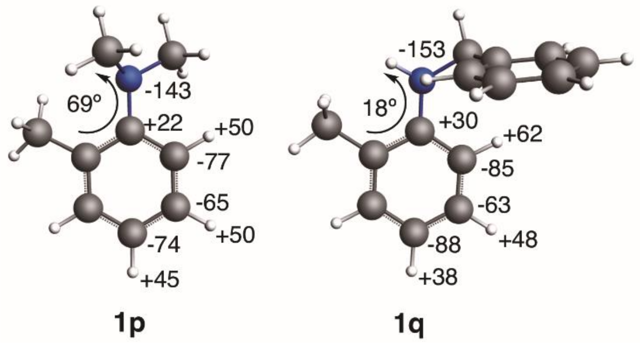
Table 5. Comparison of Pd/S,O-ligand catalyst with Ishii's catalyst.

Substrates		No ligand[a]	L[a]	Ishii's conditions[a,b]
	**3a**	18% (p:m:o = 16:1:1)	81% (p:o >19:1)	88%[c] (p:o = 13.3:1)
	**3h**	11% (p:others = 2.7:1)	70% (p:others = 10.7:1)	24% (p:others = 4.6:1)
	**3i**	11%	75% (p:o = 2.8:1)	NR
	**3m**	17% (p:others = 1.8:1)	61% (p:others = 11.2:1)	traces
	**3q**	NR	51%	NR
	**3u**	27%	70%	6%

[a] Yields and selectivities were determined by ^{1}H NMR analysis of the crude mixture using CH_2Br_2 as internal standard. [b] The reactions were performed at 60 ^oC for 2 h under a balloon of oxygen using aniline (15 mmol), ethyl acrylate (2 mmol), $Pd(OAc)_2$ (5 mol%), $H_6PMo_9V_3O_{40}.30H_2O$ (0.5 mol%) and 2,4,6-trimethylbenzoic acid (1 mmol) in DMF (2 mL). [c] Yields and site selectivities reported previously in ref 7b. NR = no reaction.

2.3. Explanation of the difference in reactivity of tertiary and secondary anilines respect to the *ortho*-substituent. As shown in Table 1, the reaction of *o*-methyl *N*,*N*-dimethylaniline (**1p**) under optimal conditions provided only traces amount of olefinated product. In contrast, *N*-benzyl *ortho*-substituted anilines were efficiently *para*-olefinated using our Pd/S,O-ligand based catalyst (Table 2). The lack of reactivity of *ortho*-substituted *N*,*N*-dialkylanilines in aromatic electrophilic substitution reactions has been observed before.[13] It has been postulated that the *ortho*-substituent clashes with the *N*-methyl group of the *N*,*N*-dimethylaniline forcing the nitrogen to twist out of the plane with the aromatic ring reducing the conjugation of the nitrogen lone pair and therefore deactivating the aniline derivative towards electrophilic aromatic substitution. To corroborate this, we calculated the torsion angle and the Voronoi deformation density (VDD) charges of **1p** and **1q** (Chart 1) at dispersion-corrected density functional theory (DFT) level (see Supporting Information).

Chart 1. Dihedral angle and VDD charges (in me.) for 1p and 1q.

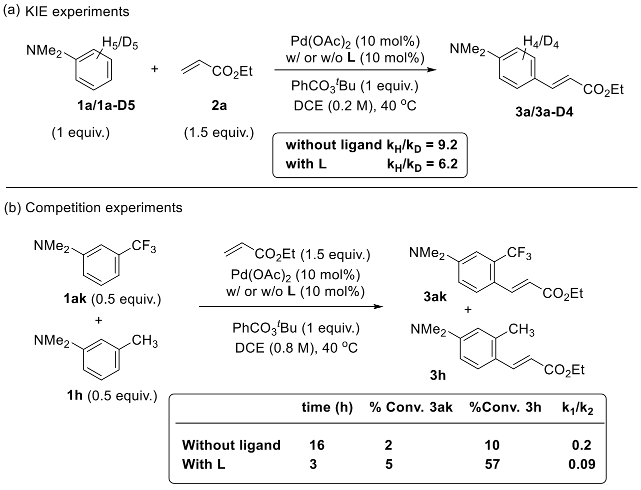


1p **1q**

In the case of *o*-methyl *N*-benzyl aniline (**1q**), the H of the NHBn almost remains in the plane (∂ = 18º), and point towards the *o*-methyl group. In contrast, one of the Me groups of the NMe2 of **1p** is twisted out of the plane (∂ = 69º) to avoid the interaction with the methyl group at the *ortho* position. As a consequence, the C atoms at the *ortho* and *para* positions of **1q** (-85 and -88 me., respectively) are more negatively charged than the equivalent ones in **1p** (-77 and -74 me., respectively). Therefore, the lack of reactivity observed in *o*-substituted *N*,*N*-dialkylanilines is a direct consequence of the lower nucleophilicity of these anilines compared with unsubstituted *N*,*N*-dialkylanilines or with *o*-substituted *N*-benzyl anilines.

2.4. Preliminary mechanistic investigations. To gain some insights into the role of the S,O-ligand in this transformation we conducted some additional experiments (Scheme 4). We considered 2 different scenarios to explain the observed acceleration in the presence of the ligand: *i*) the ligand causes a change in the mechanism of C–H bond cleavage or *ii*) the ligand accelerates the rate-limiting step. First, we determined the hydrogen/deuterium isotopic effect in the reaction with and without ligand (Scheme 4 a). Without ligand we observed a k_H/k_D of 9.2 and in the presence of the S,O-ligand (**L**) a k_H/k_D of 6.2. The observed primary kinetic isotopic effect suggests that the C–H bond cleavage is the turnover-limiting step in both cases. Furthermore, we performed intramolecular competition experiments between an electron-poor aniline, namely *N*,*N*-dimethyl-3-(trifluoromethyl)aniline (**1ak**), and an electron rich-aniline, namely *N*,*N*,3-trimethylaniline (**1h**) (Scheme 4 b). We found out that in in both cases, the most electron-rich aniline **1h** reacted preferentially. These results are consistent with two possible mechanisms: *i*) the reaction proceeds *via* an electrophilic palladation mechanism with the deprotonation of the Wheland intermediate being the rate-limiting step,[14] or *ii*) the reaction proceeds via base-assisted internal electrophilic-type substitution (BIES) mechanism.[15] At present, we cannot rule out either mechanism but it seems reasonable to postulate that the reaction proceeds via the same mechanism with and without ligand and that the S,O-ligand accelerates the C–H bond cleavage, which is the rate limiting step.

Scheme 4. Mechanistic Studies



	time (h)	% Conv. 3ak	%Conv. 3h	k_1/k_2
Without ligand	**16**	**2**	**10**	**0.2**
With L	**3**	**5**	**57**	**0.09**

3. CONCLUSION

In conclusion, we have developed the first general *para*-selective C–H olefination of aniline derivatives by Pd/S,O-ligand catalysis. The reaction proceeds under mild reaction conditions with a broad range of anilines, including mono-, di- and trisubstituted anilines bearing electron donating and withdrawing groups. In total, 42 aniline derivatives underwent *para*-selective C–H olefination in good yields using the developed methodology. We have also shown that it is possible to use oxygen as the only oxidant and that this methodology is operationally simple and scalable. The S,O-ligand is responsible for the dramatic improvements in substrate scope and the high *para*-selectivity observed in this transformation. Preliminary mechanistic studies suggest that the ligand promotes the C–H bond cleavage, which is the rate-limiting step. Further applications and mechanistic studies are currently ongoing in our laboratory

ASSOCIATED CONTENT

Supporting Information.

Experimental procedures and compounds characterization. Mechanistic studies.

Computational studies.

This material is available free of charge via the Internet at http://pubs.acs.org.

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SYNOPSIS TOC